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Synthesis of β-Amino and β-Methoxy Ketones by Lewis Acids Promoted β-Substitution Reactions of β,γ-Unsaturated Ketones

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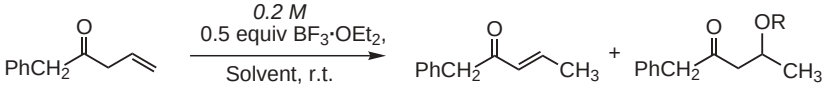
Abstract: A reaction mixture of β,γ-unsaturated ketone and $BF_3{\cdot}OEt_2$ in CH_3OH was stirred at room temperature and β-methoxy ketone was produced in high yield. The β-amino ketone was obtained as the major product from a reaction mixture of β,γ-unsaturated ketone, $AlCl_3$ and Ts-NH_2 in CH_2Cl_2 at room temperature. This Lewis acid promoted β-substitution reaction mechanism was proposed as that the process occurred via in situ isomerization of β,γ-unsaturated ketone to α,β-unsaturated ketone followed by the 1,4-addition reaction.

Key words: β,γ-unsaturated ketone, β-amino ketone, β-methoxy ketone, α,β-unsaturated ketone, 1,4-addition reaction

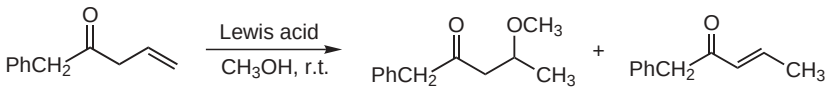
β-Alkoxy and β-amino carbonyl compounds are potentially biologically active molecules and important synthetic intermediates in organic synthesis.[1–4] Specific formation of a new bond on the β-position to the carbonyl functionality is typically produced by Aldol-type reaction,[5,6] organocopper addition reaction[7,8] and 1,4-addition reaction.[9,10] Conjugate addition of organometallic reagent to α,β-unsaturated ketone is the most direct and commonly used method for the preparation of β-substituted ketone.[11] Recently, our laboratory reported a simple and an effective method for the synthesis of β,γ-unsaturated ketone, which is the synthetic precursor of α,β-unsaturated ketone.[12] Thus, we expected that the preparation of α,β-unsaturated ketone may be achieved by the isomerization of β,γ-unsaturated ketone under mild acidic reaction condition. A reaction mixture of 1-phenylpent-4-en-2-one and Lewis acid ($BF_3{\cdot}OEt_2$) in CH_2Cl_2 was refluxed for two hours and only 40% yield of isomerized enone, 1-phenyl-pent-3-en-2-one (**I**), was obtained (Scheme 1). When the reaction mixture of 1-phenylpent-4-en-2-one and $BF_3{\cdot}OEt_2$ was stirred in CH_3OH at room temperature for two hours, 4-methoxy-1-phenylpentan-2-one was produced as the major product and isomerized enone **I** as the minor product. The reaction rate for the formation of β-alkoxy ketone decreased when the more sterically hindered ethanol was introduced under the reaction conditions. It should be noted that neither β-substitution reaction nor isomerization reaction occurred in the absence of Lewis acid and more than 98% of β,γ-unsaturated ketone was recovered even if the reaction mixture was stirred in MeOH at room temperature for 48 hours. Both Lewis acid and alcohol are necessary for the formation of β-alkoxy ketone.

The amount of Lewis acid used was investigated and the results are shown in Scheme 2. The ratio of 0.7 to 1.0



CH_2Cl_2, 2 h, reflux	**I** 40%	+	Unknowns
MeOH, 2 h	**I** 16%	+	72% (R=Me)
EtOH, 22 h	**I** 20%	+	75% (R=Et)

Scheme 1



* 0.3 $BF_3{\cdot}OEt_2$, CH_3OH, 26 h	2%	+	17% + 59% **S.M.**
* 0.7 $BF_3{\cdot}OEt_2$, CH_3OH, 2 h	86%	+	10%
* 1.0 $BF_3{\cdot}OEt_2$, CH_3OH, 2 h	89%	+	7%
* 1.5 $BF_3{\cdot}OEt_2$, CH_3OH, 2 h	70%	+	6%

Scheme 2

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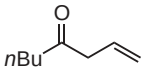
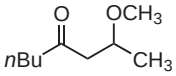
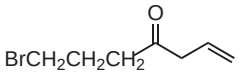
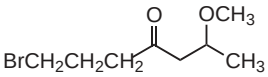
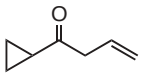
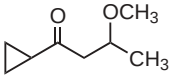
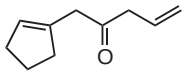
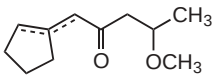
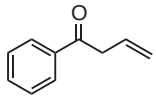
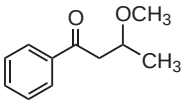
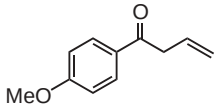
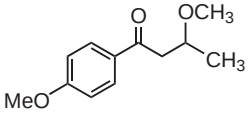
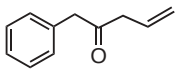
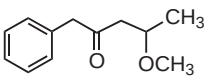
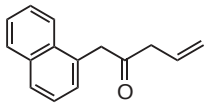
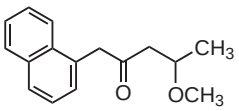
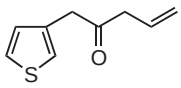
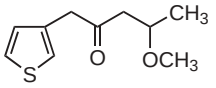
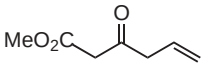
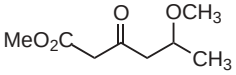
molar equivalents of Lewis acid to substrate afforded the highest yield of β-methoxy ketone. Interestingly, higher or lower ratios than this molar range led to a dramatic decrease in the yield of β-methoxy ketone obtained. The $BF_3{\cdot}OEt_2$ amount was determined to be in equal molar ratio to the substrate and it was introduced to provide the β-substitution reaction conditions. Other Lewis acids such as $AlCl_3$, $ZrCl_4$ and Me_3SiOTf also can behave as promoters for the β-substitution reactions of β,γ-unsaturated ketones. The experimental results showed that $BF_3{\cdot}OEt_2$ is the best choice of Lewis acid for the synthesis of β-methoxy ketone.

β-Methoxy of ketones are extensively observed in many naturally occurring compounds and exhibit a wide range of biological activities.[13–17] A series of β,γ-unsaturated ketones was investigated under the typical reaction conditions and the results are shown in Table 1.

All β,γ-unsaturated ketones were transformed into their corresponding β-methoxy ketones in moderate to high yields and α,β-unsaturated ketones also were generated under the reaction conditions. The β-methoxy ketones were obtained in reasonable yields even if relatively acidic α-protons existed on β,γ-unsaturated ketones (Table 1, entries 1–4, 7–10). β-Amino carbonyl compounds exhibit as an important structure in many natural products and a useful synthetic intermediate in organic synthesis.[18–23] β-Amino ketone is typically produced by the addition reaction of nucleophilic amine to α,β-unsaturated ketone in the absence of acidic α-protons. According to the results β,γ-unsaturated ketones were transformed into their corresponding β-methoxy ketones by Lewis acid promoted β-substitution reactions. This new Lewis acid promoted β-substitution reaction may provide a useful method for the synthesis of β-amino ketone under mild reaction conditions. Thus, we expected and that the relatively acidic 4-

Table 1 Synthesis of β-Methoxy Ketones

Entry	Substrate	Product	Time (h)	Yield (%)[a]
1			2	76 + 8[b]
2			2	58 + 13[b]
3			1	60
4			3	50 + 12[c]
5			3	73 + 8[b]
6			1.5	80 + 12[b]
7			2	89 + 7[b]
8			4	82 + 8[b]
9			4	77 + 7[b]
10			8	64 + 8[b]

[a] The yields were determined after chromatographic purification.
[b] The yield of isomerized enone after chromatographic purification.
[c] The yield of *endo* double bond isomer.

toluenesulfonamide (Ts-NH_2, pK_a = 16)[24,25] may possibly react as a nuclephile rather than a base under this Lewis acid promoted β-substitution reaction conditions and investigated this reaction. A reaction mixture of 1-phenylpent-4-en-2-one, $BF_3{\cdot}OEt_2$, and Ts-NH_2 in CH_2Cl_2 was stirred at room temperature for 20 hours and a very low yield (<3%) of the expected product was formed with many undetermined side products. The 47% yield of the expected β-amino ketone **A** and 28% of 1-phenylpent-3-en-2-one (**I**) were obtained when the amount of $BF_3{\cdot}OEt_2$ was decreased to 0.5 molar equivalents with respect to the substrate (Scheme 3). Other Lewis acids such as $AlCl_3$, $ZrCl_4$ and Me_3SiOTf were also investigated and $AlCl_3$ proved to be the best choice for β-amination reaction of β,γ-unsaturated ketone. The yield of β-amino ketone **A** was improved dramatically to 79% when 1.5 equivalents of Ts-NH_2 were introduced. It should be noted that the yield of β-amino ketone decreased when more than 0.5 equivalents of the amine were introduced. The best β-amination reaction conditions were determined to be 0.5 equivalents of $AlCl_3$ and 1.5 equivalents of Ts-NH_2 to 1 equivalent of substrate in CH_2Cl_2 solvent. Other more basic amines such as *n*-Bu-NH_2, Ph-NH_2, pyrrolidine and Et_2NH were investigated and none of the expected β-amino ketones were produced. Only low yields of α,β-unsaturated ketone and some unidentified side products were obtained under these reaction conditions.

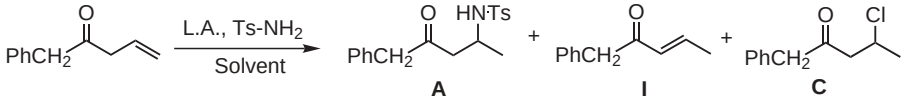
A series of β,γ-unsaturated ketones was investigated under the typical reaction conditions and the results are shown in Table 2. All β,γ-unsaturated ketones were transformed into their corresponding β-amino ketones as the major product and β-chloro ketones and α,β-unsaturated ketones as the minor products. The β-amino ketones were obtained in moderate to high yields even if relatively acidic α-protons exist on β,γ-unsaturated ketones (Table 2, entries 1–4, 7–9).

The mechanism for Lewis acid promoted formation of β-amino ketone and β-methoxy ketone from β,γ-unsaturated ketone was investigated. A reaction mixture of 1-phenylpent-3-en-2-one (**I**) and $BF_3{\cdot}OEt_2$ in MeOH was stirred at room temperature for 2 hours yielding 80% of β-methoxy ketone while 9% of the starting material was recovered (Scheme 4). The reaction mixture of 1-phenylpent-3-en-2-one (**I**), Ts-NH_2 and $AlCl_3$ in CH_2Cl_2 was stirred at room temperature for 96 hours and 65% of β-amino ketone **A** and 10% β-chloro ketone **C** were obtained. It is interesting to note that a higher yield of β-amino ketone or β-methoxy ketone was obtained by reaction with β,γ-unsaturated ketone instead of α,β-unsaturated ketone under this Lewis acid promoted β-substitution reaction conditions. The β-substitution reaction did not occur when the carbon-carbon double bond isomerization process of β,γ-unsaturated ketone was inhibited. When a reaction mixture of 1-phenyl-pent-4-en-2-one and $BF_3{\cdot}OEt_2$ in THF was refluxed for 14 hours only 21% of 1-phenyl-pent-3-en-2-one (**I**) and 66% of starting material were obtained. These results showed that the isomerization rate is much faster in MeOH than in THF. Thus, we believed that the formation of β-substituted ketone proceeded firstly by the in situ isomerization of β,γ-unsaturated ketone to α,β-unsaturated ketone followed by the 1,4-addition reaction.

In conclusion, this Lewis acid promoted β-substitution reaction of β,γ-unsaturated ketone provides a simple and highly efficient method for synthesis of β-amino and β-alkoxy ketones. The C–N and C–O bonds are selectively formed on the β-position to the carbonyl group even if the acidic α-protons exist. The extension of this reaction to differently β-substituted β,γ-unsaturated ketones and α,β-unsatured ketones using this Lewis acid promoted β-substitution reactions is underway.

Typical Procedure for the Synthesis of β-Methoxy Ketone

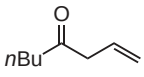
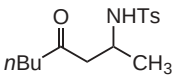
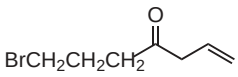
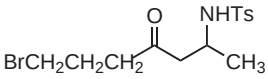
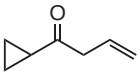
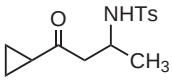
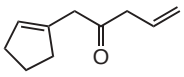
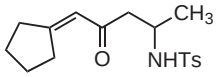
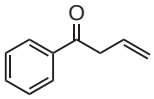
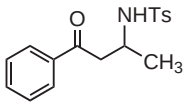
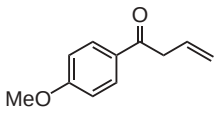
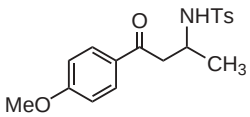
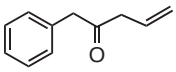
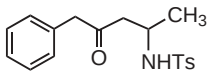
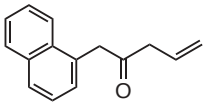
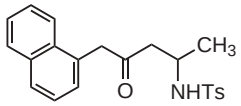
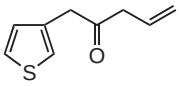
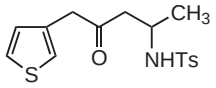
A reaction mixture of β,γ-unsaturated ketone (1.0 mmol) and $BF_3{\cdot}OEt_2$ (1.0 mmol) in anhyd CH_3OH (5 mL) was stirred at r.t. After the reaction was completed (monitored by TLC), the organic solvent was removed directly under reduced pressure. Further purification was achieved by flash chromatography with EtOAc/hexane as eluant.



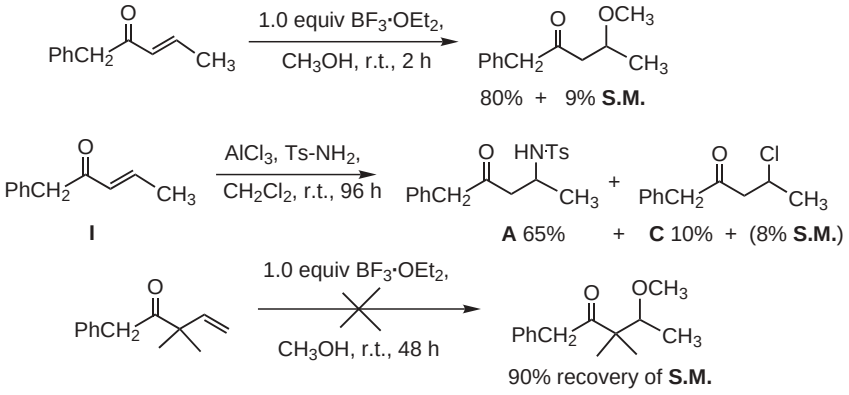
* 1.0 $BF_3{\cdot}OEt_2$, 1.0 Ts-NH_2, CH_2Cl_2, r.t., 20 h	**A** (<3%) + Unknowns
* 0.5 $BF_3{\cdot}OEt_2$, 1.0 Ts-NH_2, CH_2Cl_2, r.t., 96 h	**A** (47%) + **I** (28%)
* 0.5 $AlCl_3$, 1.0 Ts-NH_2, CH_2Cl_2, r.t., 96 h	**A** (57%) + **I** (5%) + **C** (22%)
* 0.5 $ZrCl_4$, 1.0 Ts-NH_2,CH_2Cl_2, r.t., 96 h	**A** (46%) + **C** (9%)
* 0.5 Me_3SiOTf, 1.0 Ts-NH_2, CH_2Cl_2, r.t., 96 h	**A** (28%)
* 0.7 $AlCl_3$, 1.0 Ts-NH_2, CH_2Cl_2, r.t., 96 h	**A** (55%) + **I** (6%) + **C** (14%)
* 0.5 $AlCl_3$, 1.5 Ts-NH_2, CH_2Cl_2, r.t., 96 h	**A** (79%) + **I** (4%) + **C** (12%)
* 0.5 $AlCl_3$, 2.0 Ts-NH_2, CH_2Cl_2, r.t., 96 h	**A** (60%) + **I** (3%) + **C** (16%)
* 0.5 $ZrCl_4$, 1.5 Ts-NH_2, CH_2Cl_2, r.t., 96 h	**A** (57%) + **I** (4%) + **C** (8%)

Scheme 3

Table 2 Synthesis of β-Amino Ketones

Entry	Substrate	Product	Time (h)	Yield[a]
1			78	68% (0%, 4%)[b]
2			61	51% (0%, 17%)[b]
3			48	34% (0%, 20%)[b]
4			50	39% (4%, 11%)[b]
5			50	40% (6%, 23%)[b]
6			96	69% (0%, 7%)[b]
7			96	79% (4%, 12%)[b]
8			96	66% (0%, 14%)[b]
9			50	57% (4%, 19%)[b]

[a] Yields were determined after chromatographic purification.
[b] Yields of α,β-unsaturated ketone and β-chloroketone.



Scheme 4

Typical Procedure for the Synthesis of β-Amino Ketone

The reaction mixture of β,γ-unsaturated ketone (1.0 mmol), $AlCl_3$ (0.5 mmol) and Ts-NH_2 (1.5 mmol) in anhyd CH_2Cl_2 (5 mL) was stirred at r.t. After the reaction was completed (monitored by TLC), the organic solvent was removed directly under reduced pressure. Further purification was achieved by flash chromatography with EtOAc/hexane as eluant.

Acknowledgment

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